

B. NON-TECHNICAL ABSTRACT

The general goal of this protocol is to determine the safety and feasibility of a gene therapy approach for chronic granulomatous disease (CGD). CGD is an inherited abnormality of the immune system leading to frequent infections with germs called bacteria and fungi. Normally, white blood cells called neutrophils kill these germs by making hydrogen peroxide. In some CGD patients the cellular machinery for producing this germ-killing substance is absent from the neutrophils because there is a defect in the hereditary code required to produce one protein subunit (p47^{phox}) of the machinery. Because of this, CGD patient neutrophils produce no hydrogen peroxide and cannot kill certain germs, leading to frequent life-threatening infections and premature death. While there are some treatments which can reduce infections in CGD, there is no cure for this disease except for bone marrow transplant. Bone marrow transplantation involves destroying a person's own bone marrow with drugs and irradiation and replacing it with someone else's bone marrow. This treatment can cure CGD, but is associated with high incidence of death and side effects. Gene therapy is a potential alternative to bone marrow transplant, with potential to provide a permanent correction of the CGD defect in these white blood cells. Certain blood cells called progenitor cells grow and divide to produce all the other kinds of blood cells including neutrophils. These cells will be collected and purified from the blood of CGD patients and placed in short term culture to be used for the "gene therapy". While in culture new hereditary code material (a segment of DNA, a gene) containing the code for normal p47^{phox} will be put into these progenitors using a specially modified mouse virus called a retrovirus vector. While retroviruses normally cause disease, the retrovirus vector has been altered so it can deliver new genetic material to a cell, but not cause infection. This gene therapy alters the CGD progenitors so they give rise to neutrophils capable of producing hydrogen peroxide and providing protection against infection. The "gene therapy" corrected progenitor cells will be reinfused into the CGD patient by injection into a blood vessel. It is hoped that the gene altered progenitors will find their way to the patient's bone marrow and settle in and produce normal neutrophils for some period of time. The CGD patient will not be treated to eliminate the resident defective progenitors still present in the bone marrow. These resident progenitors will dilute the effect of the smaller number of infused gene corrected progenitors, so that we expect only about 1% or less of circulating neutrophils to be corrected. However, this may be enough to provide clinical benefit. The patients will be watched for any unexpected harmful side effects that may result from this therapy. Samples of blood cells will be taken to measure the number of circulating neutrophils that produce hydrogen peroxide and to measure the presence of the new genetic material. It is hoped that this study will provide information to permit development of a safe and effective gene therapy for individuals with CGD.